Pergamon

Tetrahedron Letters 42 (2001) 7075–7078

TETRAHEDRON
LETTERS

A facile synthesis of ring-fused alkylidenecyclopropanes by olefination reaction of bicyclo[*n*.1.0]alkanone *N*,*O*-hemiacetals with Wittig reagents

Morshed Alam Chowdhury,[a] Hisanori Senboku,[a] Masao Tokuda,[a,]* Yuzuru Masuda[b] and Toshiro Chiba[b]

[a]*Laboratory of Organic Synthesis, Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan*

[b]*Department of Applied Chemistry, Kitami Institute of Technology, Kitami 090-8507, Japan*

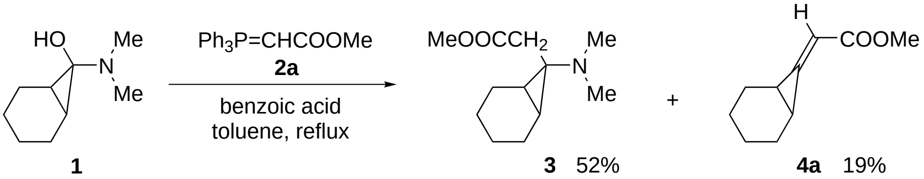
Received 16 July 2001; accepted 3 August 2001

Abstract—Ring-fused alkylidenecyclopropanes, bicyclo[*n*.1.0]alkylidene derivatives, were readily synthesized by olefination reaction of bicyclo[*n*.1.0]alkanone *N*,*O*-hemiacetals with Wittig reagents in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

Methylenecyclopropane and its derivatives are very attractive and useful substrates due to their unique reactivities originating from their highly strained structures, and they have been widely used for many kinds of organic reactions; i.e. cycloaddition reactions,[1,2] photochemical reactions,[3] and transition-metal catalyzed reactions such as silaboration,[4] diboration,[5] silylcyanation,[6] hydrosilylation,[7] hydrostannation,[8] hydroamination,[9a] hydroalkoxylation,[9b] hydrocarbonation,[9c] and other reactions.[9d–f] Due to demands for these compounds as substrates for organic reactions, facile and general methods for preparation of various kinds of methylenecyclopropane derivatives are now required.

There are many reports on the preparation of methylenecyclopropane derivatives, and these reports have recently been summarized in a review.[10] However, only a limited number of studies on preparation of ring-fused methylenecyclopropane (bicyclo[*n*.1.0]alkylidene) derivatives have been reported; i.e. reaction of alicyclic ketones with lithium trimethylsilyldiazomethane in the presence of a large excess of olefins,[11] reaction of cycloalkenes with vinylcarbenes generated from 1-chloro-2-methylpropene,[12] 5,5-dimethyl-*N*-nitrosooxazolidones,[13] or vinyl triflates[14] in the presence of a strong base, and reaction of aldehydes with α-lithio(cyclopropyl)silanes followed by treatment with *t*-BuOK.[15] These preparations, however, have several drawbacks: the use of complex reagents, strong bases, and excess olefins; long reaction time; low yields; and limitations of functional groups in substrates. There is no general method for the preparation of these unique olefins containing various functional groups.

We previously reported a facile and general method for synthesis of bicyclo[*n*.1.0]alkanone *N*,*O*-acetals and *N*,*O*-hemiacetals from enamines of cycloalkanones.[16,17]



Scheme 1.

Keywords: methylenecyclopropane; bicyclo[*n*.1.0]alkylidene derivative; Wittig reagent; bicyclo[*n*.1.0]alkanone *N*,*O*-hemiacetal; olefination.

* Corresponding author.

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(01)01449-6

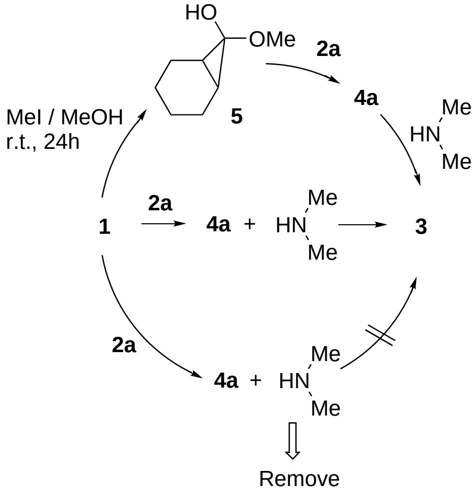
During the course of our studies on synthetic applications of those compounds, we recently found that ring-fused methylenecyclopropanes, carrying various functional groups on the C=C bond, could be readily synthesized by the reaction of the corresponding alkanone *N*,*O*-hemiacetals with Wittig reagents in one step in good yields. In this paper, we describe a convenient synthesis of six-, seven-, and nine-membered ring-fused alkylidenecyclopropanes **4, 10** and **11** by olefination reaction of the corresponding alkanone *N*,*O*-hemiacetals **1**, **6**, **7**, **8** and **9** with Wittig reagents **2**.[18]

Reaction of bicycloalkanone *N*,*O*-hemiacetal **1**, readily prepared by our procedure,[16,17] with monosubstituted Wittig reagent **2a** in the presence of a catalytic amount of benzoic acid[19] in toluene under reflux predominantly gave aminonorcarane **3**, with expected ring-fused alkylidenecyclopropane **4a** in low yield (Scheme 1).

GLC analysis of the reaction mixtures showed that a peak of **4a** appeared as a major product in the initial stage of the reaction and that its yield reached about 75% within a few minutes after the start of the reaction. However, we failed to obtain **4a** in a reasonable yield, and **3** was obtained as a final and major product. These results indicate that, in the present reaction, **4a** was formed initially and then the liberated amine immediately attacked the β-carbon of α,β-unsaturated ester **4a** to give **3** predominantly. It has already been reported that the C=C double bond of methylenecyclopropane derivatives carrying an electron-withdrawing group is reactive as a Michael acceptor.[20] Actually, a reaction of the alkylidene derivative **4a**, independently prepared from hemiacetal **5** and Wittig reagent **2a**, with amines readily afforded **3**. Accordingly, it is expected that selective formation of **4a** can be achieved by removal of the liberated amine from the reaction media as soon as it is generated (Scheme 2).

We examined the reaction of **1** with Wittig reagent **2a** in the presence of several neutral and acidic additives as shown in Table 1. When benzoic acid was used both as a catalyst and as an additive, only a complex mixture was obtained (entry 2). On the other hand, **4a** was selectively produced in moderate to good yields when the reaction was carried out in the presence of molecular sieve 4 Å, Amberlyst® 15, or *Kyowaad® 700* $(Al_2O_3 \cdot 9SiO_2 \cdot xH_2O)$[21] with a catalytic amount of benzoic acid (entries 3–10). The best result was obtained in the reaction of *N*,*O*-hemiacetal **1** with Wittig reagent **2a** in the presence of 5.7g of *Kyowaad® 700* and a catalytic amount of benzoic acid to give methyl bicyclo[4.1.0]hept-7-ylideneacetate **4a** in 82% yield (GC yield 87%) (entry 10, Table 1).

We also carried out similar reactions of norcaranone *N*,*O*-hemiacetals **1**, **6**, and **7** with monosubstituted Wittig reagents **2a**–**d** in the presence of *Kyowaad® 700* as shown in Scheme 3. In all cases, six-membered ring-fused alkylidenecyclopropanes **4a**–**d** were selectively obtained in 59–82% yields, and no aminonorcarane such as **3** was obtained.



Scheme 2.

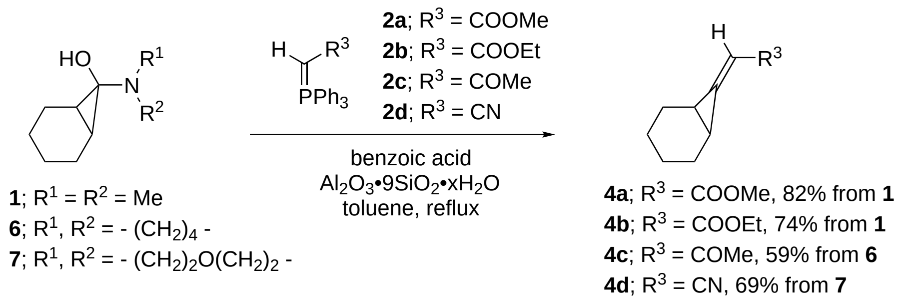
Table 1. Reactions of bicycloalkanone *N*,*O*-hemiacetal **1** with Wittig reagent **2a** in the presence of several additives[a]

Entry	Additive	Amount of additive (g)	Product yield (%)[b]	
			3	**4a**
1	None	–	52	19
2	Benzoic acid	0.98 (4 equiv.)	Trace	Trace
3	Molecular sieves 4 Å	0.6	6	45
4	Amberlyst® 15	0.2	13	53
5		0.4	Trace	58
6		0.8	0	45
7	*Kyowaad® 700*[c]	1.4	21	37
8		2.9	9	70
9		4.3	1	83
10		5.7	0	87

[a] A mixture of **1** (5 mmol), **2a** (6 mmol), and benzoic acid (0.02 g) in toluene (25 mL) was heated with additives under reflux for 2 h except for entry 1 (6 h).

[b] GC yield.

[c] $Al_2O_3 \cdot 9SiO_2 \cdot xH_2O$ (commercially available from Kyowa Chemical Industry Co., Ltd).

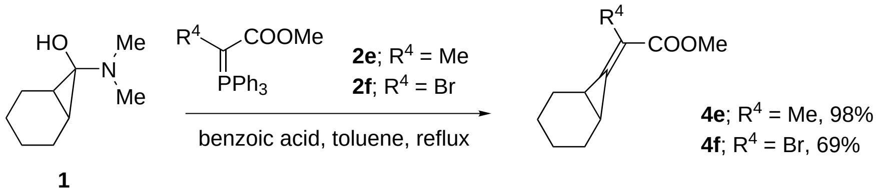


Scheme 3.

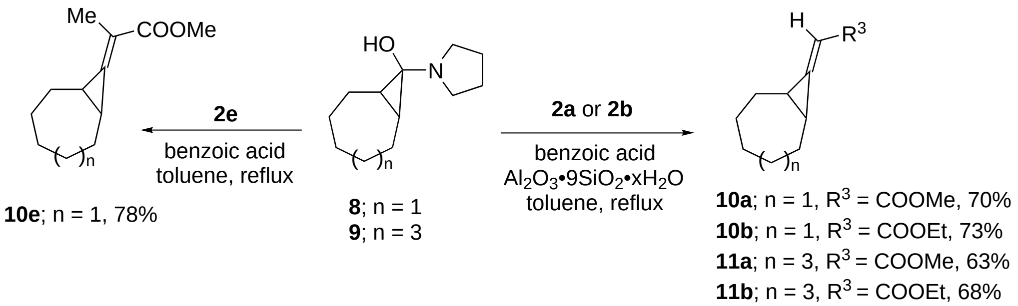
Interestingly, when disubstituted Wittig reagents **2e**–**f** were used in the reaction of **1**, substituted methylenecyclopropanes **4e**–**f** were exclusively obtained in 69–98% yields even in the absence of *Kyowaad® 700.* In these cases, no aminonorcarane was formed (Scheme 4).

By using the same procedure, we could also synthesize seven- and nine-membered ring-fused alkylidenecyclopropanes **10a**–**b**, **10e**, and **11a**–**b** in 70–78% and 63–68% yields, respectively (Scheme 5).

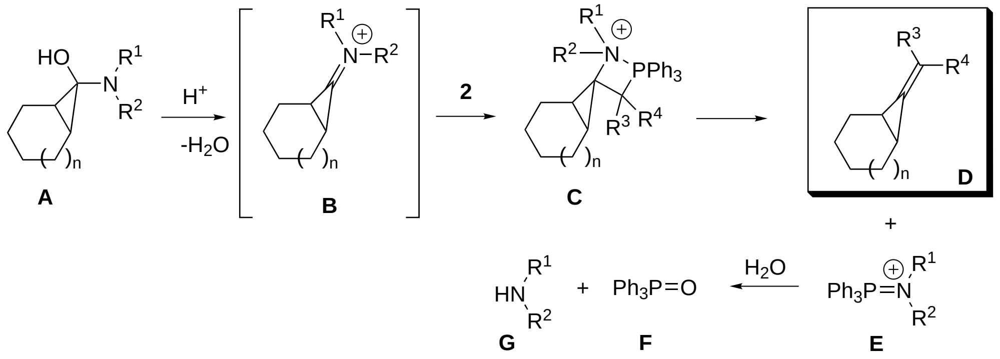
Proposed reaction pathways of the present reaction are shown in Scheme 6. The formation of ring-fused alkylidenecyclopropanes **D** proceeds probably via iminium cation **B**, which is formed from bicycloalkanone *N*,*O*-hemiacetals **A** under mild acidic conditions. Iminium cation **B** is sufficiently stable in situ to be trapped by various nucleophiles.[22] The reaction of **B** with Wittig reagent **2** gave 1:1 adducts **C**, and then elimination of an iminium salt of triphenylphosphine **E** gave **D**. Iminium salt of triphenylphosphine **E** is converted into



Scheme 4.



Scheme 5.



Scheme 6.

triphenylphosphine oxide **F** and amine **G** by reaction with water, which was produced initially during the process of formation of iminium ion **B**. Although the roles of additives are not clear, we speculate that they have the following two roles in the present reaction pathways. One is removal of liberated amines from reaction media. This effect would inhibit Michael addition of amine to a conjugated system of product **D** (see Scheme 2). Another possible role is removal of water that formed in an initial step. This effect results in no generation of amine **G**.

References

1. (a) Zorn, C.; Anichini, B.; Goti, A.; Brandi, A.; Kozhushkov, S. I.; de Meijere, A.; Citti, L. *J. Org. Chem.* **1999**, *64*, 7846–7855; (b) Thiemann, T.; Ohira, D.; Li, Y.; Sawada, T.; Mataka, S.; Rauch, K.; Noltemeyer, M.; de Meijere, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2968–2976.
2. Brandi, A.; Dürüst, Y.; Cordero, F. M.; De Sarlo, F. *J. Org. Chem.* **1992**, *57*, 5666–5670.
3. Baum, T.; Rossi, A.; Srinivasan, R. *J. Am. Chem. Soc.* **1985**, *107*, 4411–4415.
4. Suginome, M.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11015–11016.
5. Chatani, N.; Takeyasu, T.; Hanafusa, T. *Tetrahedron Lett.* **1988**, *29*, 3979–3982.
6. Ishiyama, T.; Momota, S.; Miyaura, N. *Synlett* **1999**, 1790–1792.
7. Bessmertnykh, A. G.; Blinov, K. A.; Grishin, Y. K.; Donskaya, N. A.; Tveritinova, E. V.; Yuríeva, N. M.; Beletskaya, I. P. *J. Org. Chem.* **1997**, *62*, 6069–6076.
8. Lautens, M.; Meyer, C.; Lorenz, A. *J. Am. Chem. Soc.* **1996**, *118*, 10676–10677.
9. (a) Nakamura, I.; Itagaki, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6458–6459; (b) Camacho, D. H.; Nakamura, L.; Saito, S.; Yamamoto, Y. *Angew Chem., Int. Ed.* **1999**, *38*, 3365–3367; (c) Tsukada, N.; Shibuya, A.; Nakamura, I.; Kitahara, H.; Yamamoto, Y. *Tetrahedron* **1999**, *55*, 833–8844; (d) Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y. *Angew Chem., Int. Ed.* **2001**, *40*, 1298–1300; (e) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 270–275; (f) Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 2661–2662 and references cited therein.
10. Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589–635 and references cited therein.
11. Sakai, A.; Aoyama, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 3687–3694.
12. Tanabe, M.; Walsh, R. A. *J. Am. Chem. Soc.* **1963**, *85*, 3522–3523.
13. Newman, M. S.; Patrick, T. B. *J. Am. Chem. Soc.* **1969**, *91*, 6461–6464.
14. Stang, P. J.; Mangum, M. G.; Fox, D. P.; Haak, P. *J. Am. Chem. Soc.* **1974**, *96*, 4562–4569.
15. Cohen, T.; Jung, S.; Romberger, M. L.; McCullough, D. W. *Tetrahedron Lett.* **1988**, *29*, 25–26.
16. Chiba, T.; Saitoh, I.; Okimoto, M. *Synthesis* **1999**, 1022–1026.
17. Chiba, T.; Saitoh, I.; Okimoto, M. *J. Org. Chem.* **1999**, *64*, 2516–2519.
18. The *N*,*O*-hemiacetals **1**, **6**, **7**, **8** and **9** were prepared according to our previous method.[16,17] The Wittig reagents **2a**–**f** were synthesized as described in the literature.[23] *Kyowaad® 700* was dried in an oven at 120°C overnight and used only for the reactions of **1**, **6**, **7**, **8** and **9** with monosubstituted Wittig reagents **2a**–**d**. Typically, a mixture of **1** (0.775 g, 5 mmol), **2a** (2.004 g, 6 mmol), *Kyowaad® 700* (5.7 g) and a catalytic amount of benzoic acid (0.02 g) in toluene (25 mL) was heated under reflux for 2 h. The mixture was cooled and filtered, and the filtrate was evaporated in vacuo. The residue was extracted with *n*-pentane (25 mL×3), and the combined pentane extracts were washed successively with 2N HCl, water, and saturated brine, dried over $MgSO_4$, and evaporated. The crude product was purified by column chromatography on silica gel (ether–hexane 1:1) to give methyl bicyclo[4.1.0]hept-7-ylideneacetate (**4a**) (0.681 g, 82% yield). An analytical sample of **4a** was obtained by distillation. Selected data of **4a:** Colorless liquid; bp 74–76°C (2 mmHg); IR (neat) ν 1717 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.1–1.35 (m, 4H), 1.55–2.0 (m, 6H), 3.75 (s, 3H), 6.20 (s, 1H); ^{13}C NMR (67.5 MHz): δ 12.6 (CH), 14.9 (CH), 20.9 (CH_2), 21.1 (CH_2), 21.2 (CH_2), 22.2 (CH_2), 51.2 (OCH_3), 109.6 (CH), 157.6 (C), 166.7 (CO); EIMS m/z (relative intensity) 166 (M^+, 16), 151 (32), 137 (72), 135 (40), 107 (68), 91 (99), 79 (100). Anal. calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.13; H, 8.35.
19. Benzoic acid is known to catalyze the reaction of cylopropanone hemiacetals with Wittig reagents: (a) Osborne, N. F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1435–1439; (b) Spitzner, D.; Swoboda, H. *Tetrahedron Lett.* **1986**, *27*, 1281–1284; (c) Kortmann, I.; Westermann, B. *Synthesis* **1995**, 931–933.
20. Liese, T.; Teichmann, S.; de Meijere, A. *Synthesis* **1988**, 25–32.
21. *Kyowaad® 700* ($Al_2O_3 \cdot 9SiO_2 \cdot xH_2O$) is commercially available from Kyowa Chemical Industry Co., Ltd.
22. (a) Vilsmaier, E.; Stamm, T.; Michels, G. *Synthesis* **1988**, 858–862; (b) Wasserman, H. H.; Baird, M. S. *Tetrahedron Lett.* **1971**, 3721–3724.
23. (a) Wittig, G.; Haag, W. *Chem. Ber.* **1955**, *88*, 1654–1666; (b) Ramirez, F.; Dershowitz, S. *J. Org. Chem.* **1957**, *22*, 41–45; (c) Bestmann, H. J.; Schulz, H. *Chem. Ber.* **1962**, *95*, 2921–2927; (d) Markl, G. *Chem. Ber.* **1961**, *94*, 2996–3004; (e) Denny, D. B.; Ross, S. T. *J. Org. Chem.* **1962**, *27*, 998–1000.